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(54) Title: **TOPICAL FOAMABLE PHARMACEUTICAL COMPOSITION FOR TREATING SKIN DISEASES INDUCED BY OVAL PITYROSPORUM**

(57) Abstract

A topical foamable pharmaceutical composition for treating skin diseases induced by oval Pityrosporum, containing (i) 0.1-10.0 wt %, preferably 2.1-6.0 wt % of ciclopirox or ciclopirox olamine as the antifungal active principle, and (ii) 0.5-35.0 wt %, preferably 3-20 wt % and especially 5-15 wt % of a surfactant selected from alkylbetaines, alkylamidobetaines, cocamidoalkylamines and derivatives thereof, as well as mixtures thereof.

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The present invention concerns foamable pharmaceutical compositions for topical use intended for treatment of dermatoses induced by Pityrosporum ovale.

It concerns foamable solutions or gels based on an anti-fungal active principle with a structure derived from pyridone, like, ciclopiroxolamine.

The anti-fungal agents used thus far to treat these diseases contain antibiotics of the macrolide type or other types (griseofulvine), azole derivatives, sulfur compounds, fatty acids, etc.

In therapy, local treatment remains very important and, by itself, concerns most of the cutaneous-mucosal mycoses, for which azole derivatives are most often used, which involve imidazoles (example: ketoconazole) or triazoles (example: fluconazole).

The authors are interested, in particular, in molecules with a structure derived from ciclopirox or 6-cyclohexyl-1-hydroxy-4-methyl-2-(1H)-pyridinone in the form of salts, like, ciclopiroxolamine.

These molecules are powerful anti-fungal agents, and also possess antibacterial properties. The existence of a broad spectrum permits their indication in the treatment of Tricophyton, Epidermophyton, Microsporum dermatophytoses (apart from tinea), cutaneous candidoses and pityriasis versicolor.

The present invention does not concern octopirox = piroctone = 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2(1H)-pyridinone or its active salts, which are generally used in cosmetic preparations as anti-seborrheic or anti-dandruff agents.

The invention only concerns preparations based on the salt of ciclopirox in pathologies in which Pityrosporum ovale is the principal etiological agent.

This fungus is also known under the name: Malassezia furfur, Pityrosporum orbiculare, Microsporon furfur, etc.

Generally, the treatment of a cutaneous fungal disease is only truly effective if the employed pharmaceutical specialty has two characteristics:

- an appropriate galenic form, which is the case in the treatment of pityriasis versicolor or seborrheic dermatitis, with a foamable solution or gel that permits, because of its dispersant qualities, local treatment of the body surface or scalp.
- respect of the anti-fungal activity of the active principle: as demonstrated by the present text, numerous surfactants inhibit the activity of ciclopirox derivatives.

The general objective during formulation of foamable preparations is to obtain a foam of good quality that is stable over time. To do this, one skilled in the art conventionally will use:
- a principal surfactant that permits dispersal of the active principle, creation of the foam and wetting of the surface on which it is applied,
- a secondary surfactant (or foam booster) that increases the foaming properties and stabilizes the foam.

Anionic surfactants (of the alkyl sulfate and/or alkylether sulfate type) are generally used as principal surfactant, since they have good foaming properties.

The secondary surfactants are generally anionic or amphoteric surfactants.

The nonionic surfactants are sometimes added to improve the characteristics of the foam or as a solubilizer of a perfume and/or other hydrophobic materials.

The cationic surfactants are not used very much for foaming products and are often reserved for "after shampoos" (as "conditioners").

The principal surfactants employed also belong, in particular, to the following classes (alone or in a mixture):

- monoglyceride sulfates,
- alkyl sulfonates,
- monoalkyl sulfosuccinates,

to which one adds the secondary surfactants or foam boosters:

- amine oxides,
-betaines.[1]

Thickeners, like, mineral salts, magnesium or aluminum silicate; carboxyethylcellulose, carboxymethylcellulose, can be added to stabilize the preparation over time. Sometimes humectants are also employed to reduce irritation related to the use of surfactants, especially anionic surfactants.

Numerous patents concern associations of surfactants, whose objective is to improve:

- wetting capacity (EP-A-0075994 THE PROCTOR & GAMBLE; EP-A-010556 THE PROCTOR & GAMBLE)
- or to improve foaming qualities (EP-A-0070076 THE PROCTOR & GAMBLE) of aqueous preparations.

This is not the purpose of our invention, whose foaming properties are conventionally due to the properties of the employed surfactants.

Other patents concern associations of weakly irritating surfactants for the skin (glycoside surfactant + amphoteric surfactant + foam booster), which avoid the use of a humectant or other additives in cosmetic preparations of liquid soap type for the hands or a foaming bath (U.S. Patent 4,668,422 A. E. STALEY MANUFACTURING).

Patent EP-A-0422 508 (KAO CORPORATION) describes associations of nonionic saccharide surfactants with various antibacterial agents, whose purpose is to improve the effectiveness of the anti-dandruff ingredients in shampoos. The authors explain that the type of formulation employed permits the natural defenses of the scalp relative to stimuli to be respected, because of the employed saccharide surfactants, and therefore substantially improves the antibacterial effect of the composition.

Our invention does not contain saccharide or glycoside surfactants.

Other patents describe potentiation of the activity of the anti-fungal active principle either:

- by increasing tissue penetration of the active principle (811L-064208) related to the use of an "enhancer",
- or by increasing the retention time of the anti-dandruff agent at the level of the hair and scalp:

• EP-A-0347 199 (UNILEVER PLC) concerns an aqueous shampoo with excellent foaming properties based on dialkyl sulfosuccinate, with which an anti-microbial agent is associated, chosen among the derivatives of: 1-chlorophenoxy, 1-imidazolyl-2-butanone, 1-hydroxy-2-pyridone;

• EP-A-117 135 (JOHNSON & JOHNSON) describes a detergent composition, containing a nitrogenous, water-soluble polymer + at least one anionic or amphoteric surfactant + at least one non-special anti-dandruff agent soluble in water, chosen among 1-hydroxy-2-pyridone and addition products with magnesium sulfate of 2,2'-dithio-bis-(1-pyridine oxide). According to the authors, retention at the hair level is increased by the formation of a nitrogenous, water-soluble polymer/surfactant complex (coacervate).

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[1] P ALEXANDER Spotlight on shampoos – Manufacturing chemist 61, 11, 39-43 (November 1990).

• U.S. Patent 4,835,148 (THE PROCTOR & GAMPBLE Co.) concerns shampoos for anti-inflammatory purposes, containing a water-insoluble active principle in a suspension in an aqueous vehicle (hydrocortisone acetate, pyridinethione salts, 1-hydroxy-2-pyridone) + anionic surfactants (alkyl sulfate or alkylether sulfate) + suspension agents.

The U.S. Patent 4,711,755 (HOECHST AG) and French Patent 73 25464 (FARBSWERKE HOECHST AG, formerly MEISTER LUCIUS & BRUNING) describe anti-dandruff cosmetic compositions, containing derivatives of 1-hydroxy-2-pyridone associated with various surfactants in hair products intended to be applied for a more or less long period on the scalp. These patents only claim cosmetic preparations and not pharmaceutical preparations.

The object of the present invention is not to increase the permanence of the active principles at the level of the skin or scalp. Nor does this invention concern nitrogenous, water-soluble polymers or dialkyl sulfosuccinates.

In the context of the invention, it is necessary to solubilize the employed pyridone derivatives to make pharmaceutical foamable compositions for topical use.

Ciclopirox and its derivatives are not very soluble in water.

Foamable bases that have been investigated in the context of the present invention therefore contain one or more surfactants whose function is to solubilize the active principle, and also ensure foaming qualities of the preparation.

According to the present invention, the foamable pharmaceutical composition for topical use intended for treatment of dermatoses induced by Pityrosporum ovale is characterized by the fact that it contains:

(i) as anti-fungal active principle, 0.1 to 10.0 wt.%, preferably 2.1 to 6.0%, ciclopirox or ciclopiroxolamine,

(ii) 0.5 to 35.0 wt.%, preferably 3 to 20%, and especially 5 to 15%, of a surfactant chosen from alkylbetaines, alkylamidobetaines, cocamidoalkylamines and their derivatives, as well as their mixtures.

According to another special characteristic of the invention, the composition is characterized by the fact that the surfactant is a cocamidopropylbetaine and/or cocamidopropylamine oxide.

According to the present invention, the composition is characterized by the fact that it is present in the form of a foamable gel, also containing 0.1 to 25% of a thickener and 39 to 99.3 wt.%, preferably 64 to 93.4%, and especially 69 to 91.9% water.

According to another characteristic of the present invention, the composition is characterized by the fact that a thickener is chosen among cellulose derivatives, polyethylene glycols, like, PEG 6000, ceteareth-60 myristyl glycol, as well as their mixtures.

According to the present invention, the composition is characterized by the fact that it is present in the form of a foamable aqueous solution, containing 55 to 99.4 wt.%, preferably 74 to 94.9%, and especially 79 to 92.9% water.

According to another special characteristic of the invention, the composition is characterized by the fact that it corresponds to the following composition:

Ciclopiroxolamine	4.0%
Cocamidopropylbetaine	8.0%
Cocamidopropylamine oxide	1.0%
Ceteareth-60 myristyl glycol	4.7%
Perfume	0.40%
Purified water QSP	100% W/W

According to the present invention, the composition is characterized by the fact that it corresponds to the following composition:

Ciclopiroxolamine	4.0%
Cocamidopropylbetaine	8.0%
Cocamidopropylamine oxide	1.0%
Perfume	0.4%
Purified water QSP	100% W/W

In the scope of development of a foamable gel based on ciclopiroxolamine, we prepared the following reference preparations based on ciclopiroxolamines:

Reference preparation no. 1

Ciclopiroxolamine	5%
T.E.A. lauryl sulfate	12%
Sodium C_{14}-C_{16} olefin sulfonate	5%
Hydroxyethylcellulose	0.5%
Water QSP	100%

Reference preparation no. 2

Ciclopiroxolamine	5%
Disodium lauramido MEA sulfosuccinate (and) sodium C_{12}-C_{14} olefin sulfonate	15%
Soyamide D.E.A.	3%
PEG 120 methyl glucose dioleate	2%
Water QSP	100%

Microbiological studies (see study methodology in the appendix) were carried out to compare the activity of the two formulations on Pityrosporum ovale. We were surprised to find that the activity of ciclopiroxolamine was inhibited in these two compositions.

Complementary work carried out revealed that this inhibition was solely due to the surfactants, the thickeners having no role in this inhibition.

Most foaming surfactants conventionally used for formulation of foamable gels or foamable solutions inhibit the activity of ciclopiroxolamine in vitro on *Pityrosporum ovale* (see Table 1 below).

The evaluation methodology for in vitro activity was as follows:

The recommendations of the French Pharmacopoeia, 10th Edition, concerning determination of the activity of water-miscible antiseptic preparations were applied in the context of this study.

The activity is defined by the capacity of a product to reduce the number of living cells under contact conditions representative of the therapeutic scheme.

Only some minor adaptations related to nutritive requirements of the test germ were introduced.

The operating method consisted of suspending the fungal cells in the test product, so as to obtain a maximum final product concentration, i.e., 90% in this type of test.

Contact was fixed at 5 minutes at a temperature of 32°C.

The action of the test product is then blocked by removing the product (filtration) or by dilution/neutralization.

The surviving cells are then counted on gelose plates. The difference between the initial titer of the suspension and the number of surviving cells enables us to deduce the number of killed cells.

The results are expressed in logarithms. Thus, the greater the logarithmic reduction of the populations (abbreviation: log R), the more substantial the fungal activity of the tested preparations.

The test microorganism is strain F2 of *Malassezia furfur* (synonym: Pityrosporum ovale, Pityrosporum orbiculare, etc.).

This strain is of clinical origin.

Table 1: Inactivation of ciclopiroxolamine in the presence of various surfactants on a population $> 10^6$ Pityrosporum ovale (abbreviation: P.O.)

Surfactants (CTFA name) that inhibit activity of the CPO	Activity (logarithm of reduction of population of P.O. $> 10^6$)
Reference: solution of CPO at 5%	+++
ANIONIC SURFACTANTS:	
Fatty alcohol ether sulfates	-
Fatty alcohol sulfates	-
Alkane sulfonates	-
Fatty alcohol carboxylates	-
Sulfosuccinates	-
Phosphoric acid esters	-
AMPHOTERIC SURFACTANT	-
Cocamidopropylbetaine and glyceryl laurate	-
NON-IONIC SURFACTANT	-
DEA soyamides	-

Legend:

+++: Reduction of population of P. ovale > 5 log

-: Reduction of population of P. ovale < 3 log

Surprisingly, the applicant found maintenance of the activity of ciclopiroxolamine with the surfactants of Table 2:

Table 2: Activity of ciclopiroxolamine in the presence of various surfactants on a population > 10^6 Pityrosporum ovale (abbreviation: P.O.)

Surfactants that preserve activity of CPO (CTFA name)	ACTIVITY (log of reduction) of a population of P.O. > 10^6
Reference: 5% CPO solution	+++
Cocamidopropylamine oxide	+++
Cocamidopropylaminebetaine	+++

Legend:

+++: Reduction of population of P. ovale > 5 log

Various formulations were thus produced with the ciclopirox derivatives and the aforementioned surfactants:

Example 1

Ciclopiroxolamine	2.1 to 5.0%
Cocamidopropylbetaine	5.0 to 15.0%
Dye	0.05 to 1.0%
Purified water QSP	100%

Example 2

Ciclopiroxolamine	2.5 to 6%
Cocamidopropylbetaine	5 to 15%
Ceteareth 60 myristyl glycol	0.5 to 10%
Perfume	0.01 to 2%

Purified water QSP	100%

Example 3: DC115 GM

Ciclopiroxolamine	4.0%
Cocamidopropylbetaine	8.0%
Cocamidopropylamine oxide	1.0%
Ceteareth 60 myristyl glycol	4.7%
Perfume	0.40%
Purified water QSP	100% W/W

The formulations that were developed according to these examples permit a primary cutaneous irritation index compatible with topical use; they were classified as weakly irritating or moderately irritating. These preparations are stable over time.

Table 3 compares, as an example, the activity of a gel prepared according to the following claim with the activity of ciclopiroxolamine on a strain of hospital origin F2.

Table 3: Activity or ciclopiroxolamine and the formula DC115GM on strain F2

CPO concentration	0%	1%	2%	3%	4%	5%
Log of reduction (CPO)	-	-	-	+	++	+++
Log of reduction (DC115GM)	-	-	-	+	++	+++

Legend:

-: reduction of population of P. ovale < 3 log

+: reduction of population of P. ovale between 3 and 4 log

++:reduction of population of P. ovale between 4 and 5 log

+++: reduction of population of P. ovale > 5 log

We also revealed that it is necessary to have a concentration of ciclopirox salts greater than 2.0% to have an *in vitro* activity (in 5 minutes of contact) that is interesting on P.O. (greater than 3 log of reduction).

All the conventionally employed thickeners in the formulation of foamable gels were found to be compatible in terms of activity with ciclopiroxolamine; nevertheless, for reasons of physicochemical compatibility, the present invention is limited to thickeners stable at a pH greater than or equal to 7 (the presence of CPO in the formulations causes an increase in pH, which is around 7 for preparations with 1% CPO and around 9 for preparations with 6% CPO).

CLAIMS

1. Foamable pharmaceutical composition for topical use intended for treatment of dermatoses induced by Pityrosporum ovale, characterized by the fact that it contains:

(i) from 0.1 to 10.0 wt.%, preferably 2.1 to 6.0%, ciclopirox or ciclopiroxolamine as anti-fungal active principle,

(ii) from 0.5 to 35.0 wt.%, preferably 3 to 20%, and especially 5 to 15%, of a surfactant chosen among alkylbetaines, alkylamidobetaines, cocamidoalkylamines and their derivatives, as well as their mixtures.

2. Composition according to Claim 1, characterized by the fact that the surfactant is a cocamidopropylbetaine and/or cocamidopropylamine oxide.

3. Composition according to one of the Claims 1 and 2, characterized by the fact that it is present in the form of a foamable gel, also containing 0.1 to 25 wt.%, preferably 1 to 10.0%, of a thickener and 30 to 99.3 wt.%, preferably 64 to 93.4%, and especially 69 to 91.9% water.

4. Composition according to Claim 3, characterized by the fact that the thickener is chosen among cellulose derivatives, like, ethyl and methylcellulose, polyethylene glycols, like, PEG 6000, ceteareth 60 myristyl glycol, as well as their mixtures.

5. Composition according to one of the Claims 1 and 2, characterized by the fact that it is present in the form of a foamable aqueous solution, containing 55 to 99.4 wt.%, preferably 74 to 94.9%, and especially 79 to 92.9%,water.

6. Composition according to Claim 3, characterized by the fact that it corresponds to the following composition:

Ciclopiroxolamine	4.0%
Cocamidopropylbetaine	8.0%

Cocamidopropylamine oxide	1.0%
Ceteareth 60 myristyl glycol	4.7%
Perfume	0.40%
Purified water QSP	100% W/W

7. Composition according to Claim 5, characterized by the fact that it corresponds to the following composition:

Ciclopiroxolamine	4.0%
Cocamidopropylbetaine	8.0%
Cocamidopropylamine oxide	1.0%
Perfume	0.4%
Purified water QSP	100% W/W

8. Use of an association:

(i) of 0.1 to 10.0 wt.%, preferably 2.1 to 6.0%, ciclopirox or ciclopiroxolamine and as anti-fungal active principle,

(ii) of 0.5 to 35.0 wt.%, preferably 3 to 20%, and especially 5 to 15%, of a surfactant chosen among alkylbetaines, alkylamidobetaines, cocamidoalkylamines and their derivatives, as well as their mixtures,

for preparation of a foamable pharmaceutical composition for topical use, intended for treatment of dermatoses induced by Pityrosporum ovale.

9. Use according to Claim 8, characterized by the fact that the surfactant is a cocamidopropylbetaine and/or cocamidopropylamine.